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ABSTRACT

This in vitro study compared the dose delivery and particle size distribution performance of triamcinolone acetonide from an Azmacort® metered-dose inhaler (MDI) in combination with four different spacer devices. The four spacer devices studied were the Azmacort® integrated spacer, the AeroChamber®, the InspirEase®, and the Microspacer®. For each MDI/spacer combination, at least two units from each of three lots of Azmacort were used for the determination of dose delivery and particle size distribution. The total delivery of triamcinolone acetonide was assessed using the recently proposed *United States Pharmacopeia* dosage unit sampling apparatus for MDIs at a flow rate of 60 L/min. Particle size distribution and respirable dose were assessed using the Andersen 1 ACFM Nonviable Ambient Particle Sizing Sampler (Model 20-800). The relative delivery of triamcinolone acetonide from the Azmacort integrated spacer, AeroChamber, InspirEase, and Microspacer, without a delay, was 100%, 72.9%, 16.7%, and 96.6%, respectively. Similarly, dose delivery with a 1-second delay between actuation and sample collection was 33.6%, 12.2%, 20.1%, and 22.9% of the original result, respectively. All the spacers studied changed the particle size distribution of the dose. Each spacer reduced, although not to the same degree, the deposition of triamcinolone acetonide in the throat induction port of the cascade impactor. The highest respirable dose (<5.8 μm) of triamcinolone acetonide was delivered by the Azmacort integrated spacer (68.8%), followed by the Microspacer (51.0%), AeroChamber (50.2%), and InspirEase (11.9%). Thus the Azmacort integrated spacer when used in combination with the Azmacort MDI delivered the highest total dose and greatest respirable dose of triamcinolone acetonide. The differences demonstrated in the performance (dose and particle size) among spacer devices (dose and particle size) in this in vitro study underscore the importance of evaluating drug delivery of all MDI/spacer combinations intended for drug administration. Clinical trials are needed to test the implication of the results that different MDI/spacer combinations may produce variable clinical responses in vivo. *Key words:* spacers, dose delivery, particle size, meter-dose inhaler.

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INTRODUCTION

Since their introduction in the late 1970s, spacer devices have significantly improved the delivery of aerosolized medication from metered-dose inhaler (MDI) systems. For patients with asthma, spacer devices improve depth of penetration of medication, minimize esophageal impaction and swallowing of the pharmacologic agent, and increase the total amount of respirable drug.[1–7] As a result, spacer devices can improve drug delivery to the lower respiratory tract of patients with asthma, minimize the local side effects associated with the deposition of the drug in the oropharyngeal cavity, and decrease systemic side effects associated with excessive systemic absorption of inhaled corticosteroids.[1–7]

The optimal design of an MDI (including the actuator) for a specific agent requires precise calculations based on the particle size and other physiochemical characteristics of the compound as it relates to the desired dose to be actuated from the MDI sprayhead.[8] However, most MDI canisters and spacer devices are developed and tested independently. Thus differences in MDI valve configuration, goodness-of-fit of the MDI valve and spacer device, and the aerodynamic characteristics of the spacer device all impact on the amount of drug that is eventually delivered from the spacer unit to the oropharyngeal cavity and lower respiratory tract.[8,9]

Ahrens et al[9] recently reported the performance of four MDIs alone and in combination with four spacer devices—Ace® (Diemolding Healthcare Division, Diemolding Corporation, Canastota, New York), AeroChamber® (Forest Pharmaceuticals Inc., St. Louis, Missouri), InspirEase® (Schering Corporation, Kenilworth, New Jersey), and OptiHaler® (Healthscan Products Inc., Cedar Grove, New Jersey)—by assessing drug delivery using an Andersen Cascade Impactor (Andersen Instruments, Atlanta, Georgia), a well-recognized in vitro sampling technique.[10] Although each spacer reduced the amount of drug deposited in the "throat" induction port of the apparatus, they did so to varying degrees. For example, the induction port deposition of flunisolide was decreased by 50% with the Ace, 3% with the InspirEase, 26% with the OptiHaler, and 7% with the AeroChamber as compared with the flunisolide MDI alone.[9] In contrast, the respirable dose (defined as micrograms of drug contained in particles <4.7 μm in diameter) of beclomethasone was significantly reduced by the AeroChamber, Ace, and OptiHaler compared with the beclomethasone MDI alone.[9] The InspirEase did not alter the respirable dose of beclomethasone. These results suggest that when a spacer device is used, optimal delivery of flunisolide is obtained with the AeroChamber, whereas optimal delivery of beclomethasone is achieved with the InspirEase. Because this was an in vitro study, the clinical significance of these data is unknown. The authors concluded that MDI spacers should no longer be considered universal, that is, intended for use with any MDI. Moreover, current and future spacer devices

should be tested for their effects on aerosol delivery with each MDI aerosol drug with which the manufacturer of the spacer intends them to be used.[9]

The integrated Azmacort® actuator/spacer (Rhône-Poulenc Rorer Pharmaceuticals Inc., Collegeville, Pennsylvania) has been clinically developed and tested as a unit at doses recommended for the treatment of patients with asthma.[11–13] As a result of data from clinical trials, it is known, for example, that with no delay between actuation and inhalation, a clinically active dose of triamcinolone acetonide is delivered through the integrated Azmacort spacer.[11–13] To further characterize the integrated Azmacort spacer system and to compare its performance with that of other spacer devices, an in vitro unmasked study was conducted to evaluate the total dose, particle size distribution, and respirable dose of triamcinolone acetonide delivered from an Azmacort® MDI (Rhône-Poulenc Rorer Pharmaceuticals Inc.) in combination with four different spacers.

MATERIALS AND METHODS

Three random lots of Azmacort formulated with the propellant P12 were studied. For each MDI/spacer combination, at least two random units from each of the three lots studied were selected for the determination of dose delivery or particle size distribution.

Four spacer devices were studied: (1) the Azmacort integrated actuator/spacer, a rigid cylindrical open tube spacer with a capacity of 112 mL and air inlets in the back of the device; (2) the AeroChamber, a one-way valved, cylindrical, rigid, plastic-tube holding chamber with a capacity of 145 mL measuring 11 cm in length and 4.1 cm in diameter; (3) the InspirEase, a 700-mL collapsible bag measuring 1.3 cm in length and 8.7 cm in diameter; and (4) the Microspacer® (Respiratory Delivery Systems Inc., Lowell, Massachusetts), a cylindrical, rigid, plastic tube 4.4 cm in length and 2.3 cm in diameter at one end, tapering to 2.0 cm at the other end (Figure 1). The AeroChamber and the Microspacer are not packaged with an actuator, nor do they come with a list of recommended actuators. The Azmacort sprayhead, due to its design, cannot be used with either of these spacers. To identify differences between the spacers and not be confounded by differences due to the actuators, it was necessary to identify an actuator that could produce an aerosol plume similar in character (total drug delivery and particle size distribution) to that produced by the Azmacort sprayhead. When paired with the Azmacort MDI, the total delivery of triamcinolone acetonide and the particle size distribution of the aerosol plume generated from a KN-1 actuator were determined to be similar to the Azmacort sprayhead. The AeroChamber and Microspacer were therefore paired with a KN-1 actuator distributed by Valois of America, BLM Packaging, Inc., Greenwich, Connecticut.

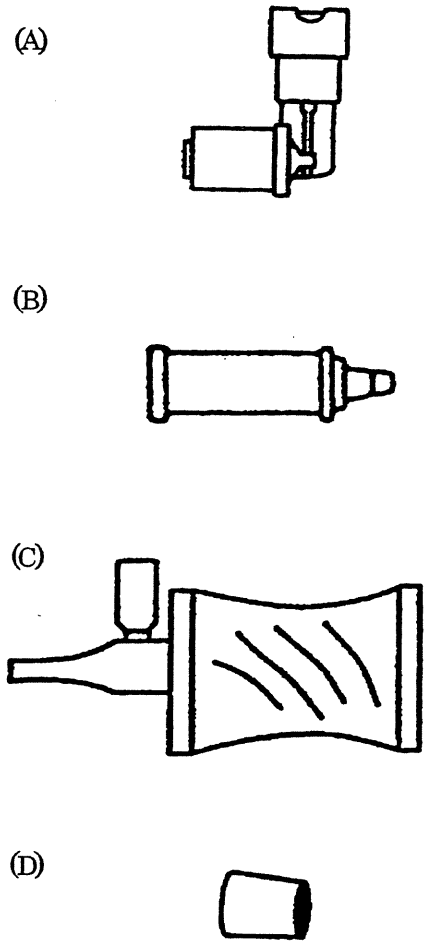

Figure 1. Schematics of metered-dose inhaler delivery systems. (A) Azmacort® integrated actuator/spacer (Rhône-Poulenc Rorer Pharmaceuticals Inc., Collegeville, Pennsylvania); (B) AeroChamber® (Forest Pharmaceuticals Inc., St. Louis, Missouri); (C) InspirEase® (Schering Corporation, Kenilworth, New Jersey); (D) Microspacer® (Respiratory Delivery Systems Inc., Lowell, Massachusetts).

Dose Delivery

The recently proposed *United States Pharmacopeia* (USP) dosage unit sampling apparatus for MDIs[14] was used at a flow rate of 60 L/min to assess the delivery of triamcinolone acetonide from the four spacers. The collection apparatus features an in-line filter designed to capture aerosolized particles. The mouthpiece of each spacer was attached to the collecting system before actuation using an adapter to prevent the loss of drug in the air and to more closely mimic the real-life situation in which the patient is instructed to place the mouthpiece of the spacer in the mouth before actuation. Deposition of drug on the filter and the walls of the collection tube (ie, dose delivered) were measured using high-pressure liquid chromatography (Table I). Each combination of the four spacers with the Azmacort MDI was tested for drug delivery with no delay and with a 1-second delay introduced between actuation and sample collection (Table II).

Table I. Chromatographic conditions for comparative study of dose delivery and particle size distribution for metered-dose inhalers.

Column	Intersil® 5 µm ODS-2, 150 mm × 4.6 mm inside diameter (Metachem Technologies, Inc., Torrance, California)
Column temperature	Ambient
Mobile phase	63:37::0.025 mol/L potassium phosphate buffer, pH 3.0: acetonitrile
Flow rate	1 mL/min
Detection	Ultraviolet absorbance at 239 nm
Injection volume	20 µL
Precision	Relative standard deviation of six replicate injections <2.0%
Run time	Approximately 10 minutes

Particle Size Distribution

The cascade impaction samples were collected with an Andersen 1 ACFM Nonviable Ambient Particle Sizing Sampler (Model 20-800, Andersen Instruments). This is an eight-stage cascade impactor with a flow rate of 28.3 L/min (±5%). A USP sample induction port was used for sample introduction.[10]

The eight-stage cascade impactor is a multiorifice device that fractionates and collects aerosol particles according to their aerodynamic diameter through serial multistage impaction. The sizes of the orifices diminish with each succeeding stage. Because the aerosol flows in sequence through successive stages, the particles captured on a given stage represent particles smaller than the cutoff size of the previous stage and larger than the cutoff stage of the given stage. Particles escaping the last stage are collected on the after-filter. The effective cutoff diameter of the orifices in stages 0 through 7 of the cascade impactor used in this study were 9.0, 5.8, 4.7, 3.3, 2.1, 1.1, 0.65, and 0.43 µm.

Table II. Dose delivery sampling scheme for each metered-dose inhaler/spacer combination tested.

Actuation	Task	Delay (s)*
0–5	Waste	—
6	Collect	0
7, 8	Waste	—
9	Collect	0
10, 11	Waste	—
12	Collect	0
13, 14	Waste	—
15	Collect	1
16, 17	Waste	—
18	Collect	1
19, 20	Waste	—
21	Collect	1

*Delay is defined as the number of seconds introduced between actuation of the metered-dose inhaler and sample collection.

The distance from the actuator mouthpiece to the back of the throat induction port was the same for all Azmacort MDI/spacer combinations. Flow was started through the cascade impactor with the induction port in place before actuation of the Azmacort MDI for each spacer combination. Before analysis, the canister was primed by shaking the inhaler vigorously for several seconds and immediately discharging a dose to waste. This procedure was repeated five times. The canister was then allowed to equilibrate to ambient temperature for 60 seconds before sample collection commenced. Using a clean delivery device, the investigator delivered three doses, shaking the inhaler in between, into the cascade impactor, allowing 30 seconds between actuations as per USP methods.[10] Deposition on the induction port was recovered with 100 mL of methanol, and the resulting solution was injected onto the high-performance liquid chromatography system as described in Table I. Stages of the cascade impactor and the after-filter were each rinsed with 10-mL methanol. The solution was sonicated for 5 minutes, mixed to achieve good washing and homogeneity, and injected onto the high-performance liquid chromatography system (Table I).

Statistical Analysis

The mean dose of triamcinolone acetonide delivered from the Azmacort MDI paired with an Azmacort actuator was labeled as 100% and all the other dose delivery values were normalized relative to this number. Data are given as mean ± SD unless otherwise indicated. A means comparison for all pairs was calculated using the Tukey-Kramer HSD method ($\alpha = 0.05$).

The respirable fraction was defined as that percentage of the total dose with particle size <5.8 μm. The respirable fraction was determined by dividing the mass of particles <5.8 μm (stages 2 through 7, plus filter) in micrograms by the total mass delivered to the impactor (induction port and stages 1 through 7, plus filter) and multiplying by 100%. The respirable dose of triamcinolone acetonide from each spacer device, with no delay, was calculated by multiplying the normalized total dose values for each device by the calculated percentage respirable fraction.

RESULTS

Dose Delivery

The mean dose of triamcinolone acetonide delivered from the Azmacort MDI, with no delay, was labeled 100% and all other dose delivery values were normalized relative to this number. The delivery of triamcinolone acetonide from the Azmacort delivery system, AeroChamber, InspirEase, and Microspacer, with no delay, was 100% (±23.0%), 72.9%

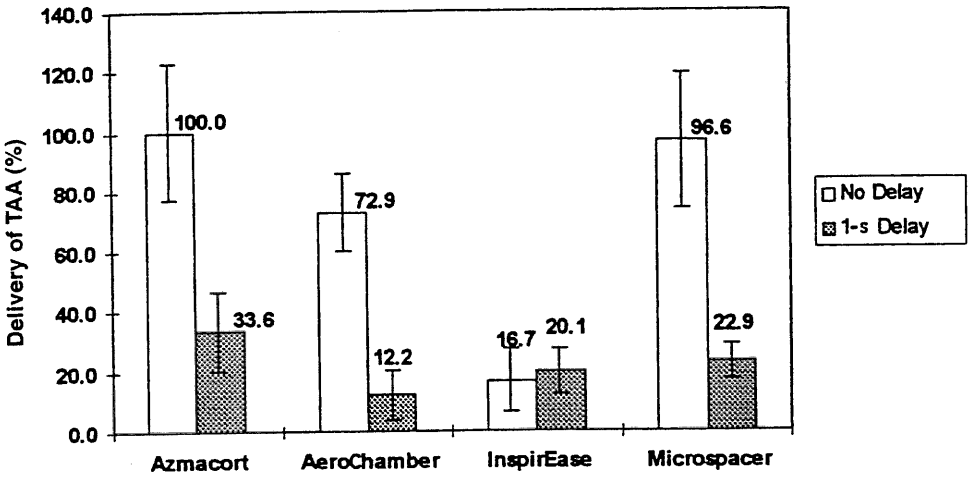

Figure 2. Delivery of triamcinolone acetonide (TAA) from four different spacers following actuation by an Azmacort metered-dose inhaler, with and without a 1-second delay. Values are normalized relative to the mean dose delivery of triamcinolone acetonide by the Azmacort integrated actuator/spacer with no delay. Azmacort® integrated actuator/spacer is a registered trademark of Rhône-Poulenc Rorer Pharmaceuticals Inc., Collegeville, Pennsylvania; AeroChamber® is a registered trademark of Forest Pharmaceuticals Inc., St. Louis, Missouri; InspirEase® is a registered trademark of Schering Corporation, Kenilworth, New Jersey; and Microspacer® is a registered trademark of Respiratory Delivery Systems Inc., Lowell, Massachusetts.

(±12.9%), 16.7% (±10.4%), and 96.6% (±22.5%), respectively (Figure 2). Performing a means comparison for all pairs using the Tukey-Kramer HSD method ($\alpha = 0.05$), no significant difference in triamcinolone acetonide delivery was shown between the Azmacort and Microspacer devices. The AeroChamber and InspirEase were determined to be significantly different from the Azmacort device ($P = 0.0001$ and $P < 0.0001$, respectively); from the Microspacer ($P = 0.0005$ and $P < 0.0001$, respectively); and from each other ($P < 0.0001$). With a 1-second delay, the dose of triamcinolone acetonide delivered from the Azmacort integrated spacer was 33.6% (±13.1%), as compared with 12.2% (±8.4%) from the AeroChamber, 20.1% (±7.5%) from the InspirEase, and 22.9% (±6.0%) from the Microspacer (Figure 2). Performing a means comparison for all pairs using the Tukey-Kramer HSD method ($\alpha = 0.05$), with a 1-second delay, the Azmacort device delivered significantly more drug substance than any other device measured ($P < 0.0001$ vs AeroChamber, $P = 0.0006$ vs InspirEase, $P = 0.0035$ vs Microspacer). The Microspacer and InspirEase were not significantly different from each other, while the AeroChamber delivered significantly less triamcinolone acetonide than the Azmacort ($P < 0.0001$) or Microspacer ($P < 0.0001$) devices with a 1-second delay.

Particle Size Distribution

When the spacer device is removed from the Azmacort delivery sys-

tem, actuation is expected to result in a large portion of the dose being deposited in the induction port (throat) of the cascade impactor. From the Azmacort sprayhead, with the spacer removed, 66.8% of the total dose of triamcinolone acetonide was deposited in the induction port of the cascade impactor. Similarly, from the KN-1 actuator alone, with no attached spacer, 69.8% of the total dose was deposited in the induction port of the cascade impactor (Table III).

The amount of triamcinolone acetonide deposited on the induction port was significantly reduced ($P < 0.0001$) with the addition of each of the four spacer devices to the Azmacort MDI. Induction port deposition with the Azmacort integrated spacer, AeroChamber, InspirEase, and Microspacer was 14.8%, 14.8%, 12.4%, and 30.8% of the total dose of triamcinolone acetonide, respectively.

The improvement in throat induction port deposition noted with the addition of the spacer devices was also seen in the respirable fraction and respirable dose (particles <5.8 μm in diameter). With the Azmacort MDI alone, the respirable fraction was 25.3% of the total dose of triamcinolone acetonide from the Azmacort sprayhead and 23.2% from the KN-1 actua-

Table III. Mean (n = 7 determinations) particle distribution of triamcinolone acetonide when delivered from an Azmacort metered-dose inhaler in combination with different spacers. Values are percentage of triamcinolone acetonide delivered to the cascade impactor by weight.

	Azmacort MDI/Device Combinations					
Variable	Azmacort Spray Head Only	KN-1 Actuator	Azmacort Integrated Spacer	AeroChamber	InspirEase	Micro-spacer
Oropharyngeal fraction (%)	74.7	76.8	31.2	31.2	28.9	47.2
Stage*						
0 (I.P., >9.0 μm)	66.8	69.8	14.8	14.8	12.4	30.8
1 (5.8–9.0 μm)	7.9	7.0	17.2	16.4	16.5	16.4
Respirable fraction (%)†	25.3	23.2	68.8	68.8	71.1	52.8
Stage*						
2 (4.7–5.8 μm)	7.3	7.2	18.4	17.7	18.9	16.3
3 (3.3–4.7 μm)	9.4	8.7	27.3	25.2	27.1	18.8
4 (2.1–3.3 μm)	4.1	3.5	11.3	10.7	11.0	8.0
5 (1.1–2.1 μm)	2.0	1.7	5.2	6.5	6.0	3.9
6 (0.7–1.1 μm)	1.4	1.1	3.9	4.7	4.4	2.9
7 (0.4–0.7 μm)	0.6	0.5	1.6	2.1	2.0	1.5
Filter paper (<0.4 μm)	0.5	0.5	1.1	1.8	1.7	1.5

Note: Azmacort® integrated actuator/spacer is a registered trademark of Rhône-Poulenc Rorer Pharmaceuticals Inc., Collegeville, Pennsylvania; AeroChamber® is a registered trademark of Forest Pharmaceuticals Inc., St. Louis, Missouri; InspirEase® is a registered trademark of Schering Corporation, Kenilworth, New Jersey; and Microspacer® is a registered trademark of Respiratory Delivery Systems Inc., Lowell, Massachusetts.

I.P. = induction port of cascade impactor.

*Particles separated according to size by use of an 8-stage cascade impactor; parenthetic value is size of trapped particles.

†Respirable fraction is defined as percentage of particles (<5.8 μm).

tor. The addition of the Azmacort integrated spacer improved the respirable fraction to 68.8% of the total dose of triamcinolone acetonide. Similarly, AeroChamber, InspirEase, and Microspacer improved the respirable fraction to 68.8%, 71.1%, and 52.8% of the total dose of triamcinolone acetonide, respectively. The respirable dose, calculated by multiplying the total dose of triamcinolone acetonide delivered from each device with no delay by the respirable fraction, from the Azmacort delivery system, the AeroChamber, InspirEase, and Microspacer was 68.8%, 50.2%, 11.9%, and 51.0%, respectively (Figure 3, Table IV).

Performing a means comparison for all pairs using the Tukey-Kramer HSD method ($\alpha = 0.05$), the Azmacort device delivered a significantly greater respirable dose of triamcinolone acetonide than the AeroChamber ($P = 0.0001$), InspirEase ($P < 0.0001$), or Microspacer ($P = 0.0005$). The respirable dose from the Microspacer and AeroChamber was statistically equivalent, while the respirable dose from the InspirEase was significantly less than any other device characterized ($P < 0.0001$ for all comparisons).

DISCUSSION AND CONCLUSIONS

The results of this in vitro study demonstrate that the Azmacort integrated

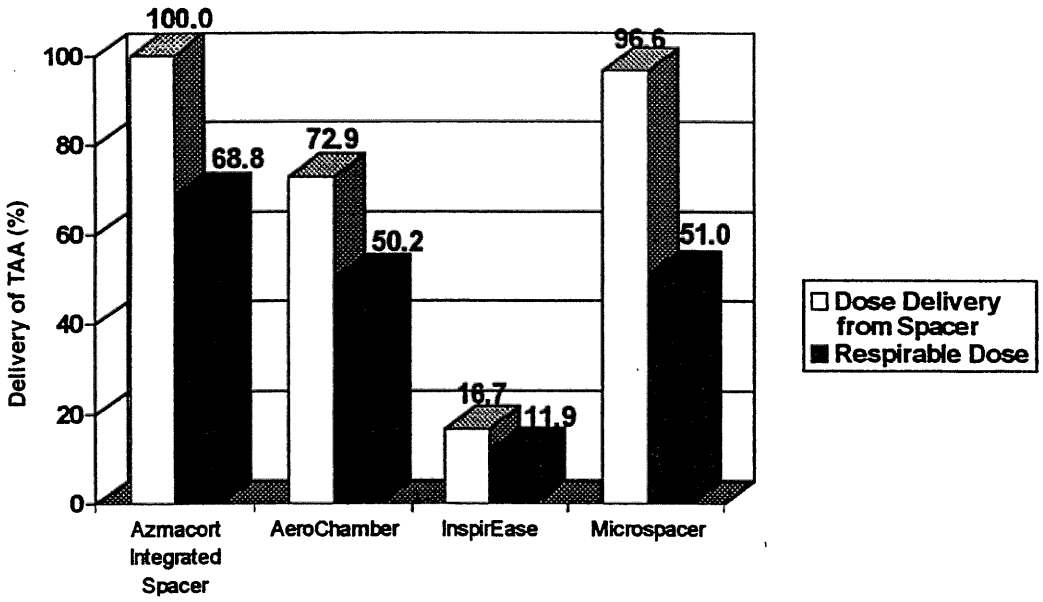

Figure 3. Total dose delivery and respirable dose (particles <5.8 μm) of triamcinolone acetonide (TAA) from four different spacer devices following actuation by an Azmacort metered-dose inhaler with no delay. Values are normalized relative to the mean dose delivery of triamcinolone acetonide by the Azmacort integrated actuator/spacer with no delay. Azmacort® integrated actuator/spacer is a registered trademark of Rhône-Poulenc Rorer Pharmaceuticals Inc., Collegeville, Pennsylvania; AeroChamber® is a registered trademark of Forest Pharmaceuticals Inc., St. Louis, Missouri; InspirEase® is a registered trademark of Schering Corporation, Kenilworth, New Jersey; and Microspacer® is a registered trademark of Respiratory Delivery Systems Inc., Lowell, Massachusetts.

Table IV. Delivery of triamcinolone acetonide from an Azmacort metered-dose inhaler (MDI) in combination with different spacers.

	Triamcinolone Acetonide Delivered with No Delay (%)*	% Respirable Fraction	Respirable Dose %
Azmacort integrated spacer	100.0	68.8	68.8
AeroChamber	72.9	68.8	50.2
InspirEase	16.7	71.1	11.9
Microspacer	96.6	52.8	51.0

Note: Azmacort® integrated actuator/spacer is a registered trademark of Rhône-Poulenc Rorer Pharmaceuticals Inc., Collegeville, Pannsylvania; AeroChamber® is a registered trademark of Forest Pharmaceuticals Inc., St. Louis, Missouri; InspirEase® is a registered trademark of Schering Corporation, Kenilworth, New Jersey; and Microspacer® is a registered trademark of Respiratory Delivery Systems Inc., Lowell, Massachusetts.
*Normalized relative to the delivery of triamcinolone acetonide from an Azmacort MDI in combination with an Azmacort integrated actuator/spacer.

spacer delivered the most triamcinolone acetonide with or without a 1-second delay. As expected, the addition of spacer devices to the Azmacort MDI had a significant effect on the amount of triamcinolone acetonide delivered, as well as the deposition of drug throughout various parts of the in vitro respiratory system. Results of the cascade impaction testing also showed that the four spacer devices, in general, decreased the deposition of triamcinolone acetonide in the "throat" induction port. Furthermore, the pairing of each spacer device to the Azmacort MDI increased the amount of drug available for deposition in the lungs compared with when no spacer was used.

As noted in Figure 2, there were considerable differences among the spacer devices used in this study with regard to the amount of triamcinolone acetonide delivered and the resultant respirable dose. These results are consistent with those of Ahrens et al,[9] who also noted differences in the dose delivery of four different spacer devices and four MDIs.

In conclusion, the Azmacort integrated spacer, when used in combination with the Azmacort MDI, delivered the most total dose and greatest respirable dose of triamcinolone acetonide as compared with the AeroChamber, InspirEase, and Microspacer. Furthermore, the differences in performance among spacer devices demonstrated in this in vitro study underscore the importance of evaluating in vitro drug delivery of all non-integrated spacer-MDI combinations. While the clinical significance of this in vitro study has not been determined, the findings strongly support the need for all spacer-MDI combinations to be well characterized in vitro as well as in vivo.

Acknowledgment

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